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EDITORIAL COMMENT

Building the Case for Central Blood Pressure*

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The epidemiology of high blood pressure (BP) in the community has relied on conventional readings utilizing cuff-based measurements of the brachial artery. Beyond establishing relationships between BP and major clinical events, clinical trials have provided data regarding the levels of BP at which antihypertensive treatment can reduce adverse cardiovascular outcomes. Now, beyond these approaches, a paper in this issue of the *Journal* by Chen et al. (1) provides valuable background data for central BP.

See page 1780

Can central BP enhance clinical practice? The principal phenotype of hypertension in the aging population is linked to the hemodynamic effects of aortic stiffening, so, central BP analyses could provide valuable guidance in understanding and managing this common condition.

Central (aortic) BP is an enticing concept. The 3 major target organs of hypertension—the central nervous system; the heart, including both the left ventricle and the coronary circulation; and the kidneys—are connected to the aorta. It has been observed that BP readings in the brachial artery are not exactly representative of central BP because of an amplification effect that augments the peripheral BP (2,3). Moreover, the degree of augmentation varies considerably among individuals (4,5). All the same, we cannot be certain that the arteries linking the central circulation to these organs are not affected by adaptive processes that could also result in BPs that differ from the aortic readings. Indeed, the circulation in both the brain and the kidney are governed by powerful autoregulatory processes that modify internal BP.

A study that has drawn strong attention to the potential superiority of central BP is the CAFE (Conduit Artery Function Evaluation) substudy of the ASCOT (Anglo Scandinavian Cardiac Outcomes Trial) (6). The main ASCOT trial originally reported that the calcium channel blocker, amlodipine, had superior cardiovascular stroke and survival benefits to the beta-blocker, atenolol, despite apparently similar effects of these drugs on arm BP. In the CAFE substudy, despite nearly identical effects of the drugs on brachial BP, amlodipine had a significantly greater effect than atenolol in reducing central BP, thus suggesting that this BP value was the pivotal factor in cardiovascular protection (6). The practical importance of this observation, however, had been somewhat diminished because although the antihypertensive action of the conventional beta-blocker atenolol, as with other conventional beta-blockers (7), was clearly less in the central circulation than at the brachial artery, this finding does not seem to apply to newer vasodilating agents in this class (7) and does not appear to have been observed with other antihypertensive classes.

Building on studies such as CAFE, central BP values have been more predictive of vascular disease and major clinical events than brachial BP in several studies (8,9) and offer the opportunity of refining our estimation of cardiovascular risk. One obstacle in the more widespread usage of this technique is the need for reference standards.

Establishing thresholds. If central BP is to play a part in the diagnosis and therapy of hypertension, it is critical to establish criteria for guiding clinical decisions. The new report by Chen et al. (1) seeks to address this need. The work of these investigators is based on prospective longitudinal studies of central BPs in 2 independently recruited cohorts of volunteers in Taiwan. The first of these was a derivation cohort from which diagnostic thresholds were established, and the second was a validation cohort in which the findings from the first cohort could be tested further.

The derivation cohort was composed of subjects who, using standard BP methods, were normotensive or, if hypertensive, were not receiving treatment. They were aged between 30 and 79 years. Subjects were excluded if they had a history of cardiovascular or stroke events. The validation cohort was slightly older (a mean age of 54 vs. 52 years in the derivation cohort), had lower arm and central BP values, and had a greater prevalence of dyslipidemia. The central BPs were measured by a method based on carotid tonometry in the derivation cohort and by radial artery tonometry using a generalized transfer function in the validation cohort. The main endpoint of the study was mortality and its causes. This was assessed by matching the databases of the 2 cohorts with the National Death Registry in Taiwan.

Based on sophisticated statistical modeling, the authors propose that optimal central BP be 110/80 mm Hg and that

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130/90 mm Hg be the threshold for hypertension. Using these values, they reported highly significant hazard ratios based on systolic BPs for cardiovascular death, total death, and stroke death. By comparison, the use of systolic BPs measured in the brachial artery was predictive of total death and stroke death, but not cardiovascular death.

Interpreting the findings. There should be some care in generalizing the findings of this research. These observations were conducted in Taiwanese subjects, and it would be useful to obtain confirmatory evidence in other populations. Furthermore, the subjects did not have known clinical cardiovascular disease, which is acceptable in describing the natural history of BP values, but not necessarily relevant to patients in clinical practice. The endpoints for the study were all related to mortality, an understandable limitation, given the fact that event rates were obtained from a death registry. All the same, it is quite possible that nonfatal coronary, stroke, and renal findings might depend on different central BP thresholds.

Another issue with central BP is the proliferation of measurement devices. Even in the paper by Chen et al. (1), 2 different methods were used, although each of them has been validated (10,11). Apart from intrinsic variations in the measurements provided by different instruments, some of them—particularly those depending on applanation tonometry—are operator dependent, and so require skill and experience. The cuff methods that are used for central BP use oscillometric technology, which again requires care and consistency in their use. In addition, most methods depend on obtaining peripheral pulse waves that are then translated into central BPs by proprietary algorithms. Although the results may be reproducible for a given device, variations between instruments may make it difficult to compare their data. It should be acknowledged that this problem is not unique to central BP. Conventional office readings, either manual or by automated monitors, are also subject to between-method variability.

Finding a clinical context. The work by Chen et al. (1) in establishing thresholds is a vital step in a broader use of central BP in research and in clinical practice. This new information is reminiscent of the Prospective Studies Collaboration that links conventional office BPs to coronary and stroke mortality (12). In that database, the lowest event rates were at 115/75 mm Hg and doubled with each 20/10 mm Hg increment after that. But although these data help in describing the natural history of people with high BP, they have limited clinical applicability. Simply put, they describe the outcomes of naturally found BPs, but cannot inform us whether reducing BP in hypertensive patients will produce the low event rates predicted by the epidemiology.

Because of this uncertainty, major guidelines pragmatically define hypertension as that level of BP at which there is clinical trial evidence that therapeutic interventions reduce cardiovascular event rates (13,14). Based on conventional readings, there is evidence of benefit when systolic BPs are reduced from above to below 160 mm Hg (15) and from above to below 150 mm Hg (16). Ironically, the most widely recommended threshold of 140 mm Hg has not been based on prospective clinical trials designed to test this value, but analysis of on-treatment cardiovascular, stroke, and renal event rates in several authoritative studies has indicated outcomes benefits when systolic BP is reduced below 140 mm Hg (17–19). Further reduction below 130 mm Hg, the central BP threshold suggested by Chen et al. (1), appears to be safe but has not been shown to provide further benefit.

How can the new central BP thresholds be used? Ongoing randomized clinical trials with cardiovascular outcomes to test the validity of 130 mm Hg or other threshold values during hypertension therapy will be critical in confirming the role of central BP. Additionally, prospective therapeutic trials that relate central BPs to carefully selected surrogate vascular endpoints could build a portfolio of evidence to further advance interpretation of central BPs. Even so, we believe we are now at a point where central BP should emerge, not only as a key endpoint in research studies, but also as a measurement of growing interest and value to clinicians.

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